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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/579,605 | 05/17/2006 | Shun-ichi Harada | 21350YP | 9392 |

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| EXAMINER | |
|---|---|
| GAMETT, DANIEL C | |
| ART UNIT | PAPER NUMBER |
| 1647 | |
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| 10/10/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/579,605 | HARADA ET AL. | |
| | Examiner | Art Unit | |
| | DANIEL C. GAMETT | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 3-16* is/are pending in the application.

4a) Of the above claim(s) *3-9 and 11* is/are withdrawn from consideration.

5)☒ Claim(s) *10* is/are allowed.

6)☒ Claim(s) *12-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. The amendments of 06/26/2008 have been entered in full. Claims 2 and 17-38 are cancelled. Claims 1, 3-9, and 11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claims 10 and 12-16 are under examination.

2. All prior objection/rejections not specifically maintained in this office action are hereby withdrawn.

3. The indicated allowability of claims 12-16 is withdrawn in view of the newly discovered reference(s) to WO200292015 and US Patent Application No. 20040038860 (Allen). Rejections based on the newly cited reference(s) follow.

### *Claim Rejections - 35 USC § 102*

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 12, 13, 15, and 16 are rejected under 35 U.S.C. 102 (a and e) as being anticipated by WO200292015 (Allen), published November 21, 2002, filed May 17, 2002, and under 35 U.S.C. 102(e) US Patent Application Publication No. 20040038860, which is the U.S.

National stage entry of WO200292015. Allen qualifies as prior art under 102(a) reference because of its publication date and under 102(e) because of its filing date.

6. Claims 12, 13, 15, and 16 are drawn to a method for determining whether an analyte is an antagonist of Dickkopf 1 (Dkk-1) comprising: (a) providing a polypeptide comprising the extracellular domain of a Dkk-1 receptor; (b) contacting the polypeptide with a rhesus monkey Dkk-1 (rhDkk-1) and the analyte; and (c) determining whether binding of the rhDkk-1 to the polypeptide is decreased in the presence of the analyte, wherein a decrease in the binding indicates that the analyte is an rhDkk-1 antagonist. Claims 13, 15, and 16 which depend on claim 12 are further drawn to the method of claim 12, wherein the Dkk-1 receptor is low-density lipoprotein receptor related protein 5 (LRP5) or low density lipoprotein receptor related protein 6 (LRP6) and wherein the rhDkk-1 is labeled and wherein the rhDkk-1 is a fusion protein. Step (b) of the claim requires contacting the polypeptide receptor with rhesus monkey Dkk-1 (rhDkk-1) and analyte. The claim does not define rhDkk-1 by any particular structure or function. The specification defines the term in ambiguous terms. Paragraph 43 of the published application) defines the term by origin of the protein without any structural functional feature. It states:

> "The term "rhDkk-1 protein" means that the rhDkk-1 protein is of rhesus monkey origin, either isolated from rhesus monkey tissue, produced from a nucleic acid obtained from the rhesus monkey by recombinant means, produced from a nucleic acid synthesized in vitro but which encodes the rhDkk-1 protein, or synthesized in vitro. The term further includes biologically active fragments or portions of the rhDkk-1 protein."

Also, paragraphs 76-77 state:

> [0076]"In further aspects of the present invention, rhDkk-1 proteins are provided which have an amino acid sequence which is substantially similar to the amino acid sequence set forth SEQ ID NO:2 and nucleic acids which encode the rhDkk-

> 1 proteins for use in the analyte screening assays disclosed herein. Further provided are nucleic acids encoding the rhDkk-1 protein which have a nucleotide sequence substantially similar to the nucleotide sequence set forth in SEQ ID N0:l. As used herein, the term "substantially similar" with respect to SEQ ID NO:2 means that the rbDkk- 1 protein contains mutations such as amino acid substitution or deletion mutations which do not abrogate the ability of the rhDkk-1 protein to bind at least one of its receptors and suppress or inhibit Wnt signaling. The mutations include naturally occurring allelic variants and variants produced by recombinant DNA methods. As used herein, the term "substantially similar" with respect to SEQ ID NO:1 means that the rhDkk-1 protein encoded by the nucleic acid contains mutations such as nucleotide substitution or deletion mutations which do not abrogate the ability of the rhDkk-1 protein to bind at least one of its receptors and suppress or inhibit Wnt signaling. The mutations include naturally occurring allelic variants and variants produced by recombinant DNA methods. In general, any of the foregoing mutations which do not abrogate the ability of rhDkk-1 protein to bind at least one of its homologous or heterologous Dkk-1 receptors are conservative mutations.
>
> [0077]The present invention further includes biologically active fragments or mutants of SEQ ID N0:l. Any such biologically active fragment and/or mutant will encode either a polypeptide or polypeptide fragment which at least substantially mimics the properties or activity of the rhDkk-1 protein, including but not limited to the rhDkk-1 protein as set forth in SEQ ID NO:2. Any such polynucleotide includes, but is not limited to, nucleotide substitutions, deletions, additions, amino-terminal truncations, and carboxy-terminal truncations which do not substantially abrogate the properties or activities of the rhDkk-1 protein produced therefrom. Thus, the mutations of the present invention encode mRNA molecules that express a rhDkk-1 protein in a eukaryotic cell which has sufficient activity (ability to bind one or more of its receptors) to be useful in drug discovery.

7. Thus, the broadest reasonable interpretation of the phrase "rhDkk-1" is a protein that is homologous to rhDkk-1" and binds to a Dkk-1 receptor. Allen discloses a Dkk-1 polypeptide (SEQ ID NO:128) which is 98.5% identical to SEQ ID NO: 2 (see below for sequence comparison). Allen further discloses methods of identifying compounds that inhibit the interaction of Dkk-1 and its receptor, in particular, LRP5 or LRP6; the methods may employ the ligand binding domain (extracellular) of the receptor and/or Dkk fusion proteins or

labeled Dkk (see pages 14-17 and 129-130 of WO200292015). Allen, therefore, teaches using a polypeptide that is indistinguishable form rhDkk-1, as claimed, in methods that are identical to those recited in the instant claims.

8. RESULT 11

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ADE82552
ID   ADE82552 standard; protein; 266 AA.
XX
AC   ADE82552;
XX
DT   15-JUN-2007  (revised)
DT   29-JAN-2004  (first entry)
XX
DE   Human protein sequence related to the invention #24.
XX
KW   LRP5; LRP6; HBM; Dkk activity; Osteopathic; Antiinflammatory;
KW
OS   Homo sapiens.
XX
PN   WO200292015-A2.
XX
PD   21-NOV-2002.
XX
PF   17-MAY-2002; 2002WO-US015982.
XX
PR   17-MAY-2001; 2001US-0291311P.
PR   01-FEB-2002; 2002US-0353058P.
PR   04-MAR-2002; 2002US-0361293P.
XX
PA   (GENO-) GENOME THERAPEUTICS CORP.
PA   (AMHP ) WYETH.
XX
PI   Allen K,  Anisowicz A,  Bhat BM,  Damagnez V,  Robinson JA;
PI   Yaworsky PJ;
XX
DR   WPI; 2003-129219/12.
DR   PC:NCBI; gi7110719.
DR   PC:SWISSPROT; O94907.
DR   PC:BIND; 150549.
XX
PT   Regulating LRP5, LRP6 or HBM activity in a subject, useful for
modulating
PT   lipid levels and/or bone mass, and for in treating bone mass disorders,
PT   e.g. osteoporosis, comprises administering a composition which modulates
PT   a Dkk activity.
XX
PS   Disclosure; SEQ ID NO 128; 173pp; English.
XX
CC  The present invention relates to regulating LRP5, LRP6 or HBM activity in
```

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CC   a subject comprising administering a composition which modulates a Dkk
CC   activity. The method is useful for modulating lipid levels and/or bone
CC   mass, and is useful in treating or diagnosing abnormal lipid levels and
CC   bone mass disorders, such as osteoporosis, bond fracture, age-related
CC   loss of bone, a chondrodystrophy, drug-1nduced bone disorder, high bone
CC   turnover, hypercalcaemia, hyperostosis, osteogenesis, imperfecta,
CC   osteomalacia, osteomyelitis, Paget's disease, osteoarthritis, and
CC   rickets. Modulators of Dkk activity are useful for as reagents in
CC   studying bone mass and lipid level modulation, in modulating Wnt
CC   signaling, or treating Dkk-mediated disorders. The present sequence
CC   represents a human protein sequence related to the invention.
CC
XX
SQ   Sequence 266 AA;

  Query Match             98.5%;  Score 1438;  DB 6;  Length 266;
  Best Local Similarity   97.7%;  Pred. No. 3.1e-120;
  Matches  260;  Conservative    4;  Mismatches    2;  Indels    0;  Gaps
0;

Qy          1 MMALGAAGAARVLVALVAAALGGHPLLGVSATLNSVLNSNAIKNLPPPLGGAAGHPGSAV 60
              ||||||||| || ||:||||||||||||||||||||||||||||||||||||||||||||
Db          1 MMALGAAGATRVFVAMVAAALGGHPLLGVSATLNSVLNSNAIKNLPPPLGGAAGHPGSAV 60

Qy         61 SAAPGILYPGGNKYQTIDNYQPYPCAEDEECGTDEYCASPTRGGDAGVQICLACRKRRKR120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 SAAPGILYPGGNKYQTIDNYQPYPCAEDEECGTDEYCASPTRGGDAGVQICLACRKRRKR120

Qy        121 CMRHAMCCPGNYCKNGICVSSDQNNFRGEIEETITESFGNDHSTLDGYSRRTTLSSKMYH180
              |||||||||||||||||||||:|||||||||||||||||||||||||||||||||||||
Db        121 CMRHAMCCPGNYCKNGICVSSDQNHFRGEIEETITESFGNDHSTLDGYSRRTTLSSKMYH180

Qy        181 SKGQEGSVCLRSSDCATGLCCARHFWSKICKPVLKEGQVCTKHRRKGSHGLEIFQRCYCG240
              :||||||||||||:|||||||||||||||||||||||||||||||||||||||||||||
Db        181 TKGQEGSVCLRSSDCASGLCCARHFWSKICKPVLKEGQVCTKHRRKGSHGLEIFQRCYCG240

Qy        241 EGLSCRIQKDHHQASNSSRLHTCQRH 266
              ||||||||||||||||||||||||||
Db        241 EGLSCRIQKDHHQASNSSRLHTCQRH 266
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***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claim 14 rejected under 35 U.S.C. 103(a) as being unpatentable over WO200292015 (Allen) or U. S. Publication No. 20040038860 as applied to claims 12, 13, 15, and 16 above, and further in view of US 20050244826 (Niehrs), filed March 28, 2003.

11. As noted, Allen teaches using a polypeptide that is indistinguishable from rhDkk-1, as claimed, in methods that are identical to those recited in the instant claims. These methods include methods of identifying compounds that inhibit the interaction of Dkk-1 and its receptor, in particular, LRP5 or LRP6. Allen does not disclose, however, methods wherein the Dkk receptor is kremen1 or kremen2 as recited in instant claim 14. Niehrs identified kremen1 or kremen2 as receptors for Dkk-1 and proposed that they may be drug targets allowing the identification of compounds useful for therapy [0017]. Niehrs further teaches assays to modulate the interactions among Dkk, kremen, and other components of wnt signaling [0049, 0056, 0060]. Therefore, in view of Niehrs, one of skill in the art would be motivated and expect success in employing kremen, or Dkk-binding fragments thereof, in methods analogous to those taught in Allen, to arrive at the method of instant claim 14. Therefore, the method recited in claim 14 is prima facie obvious in view of the combined teaching of the cited prior art.

***Conclusion***

12. Claim 10 is allowable.

13. Claims 12-16 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571 272 0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/D. C. G./
Examiner, Art Unit 1647

/David S Romeo/
Primary Examiner, Art Unit 1647